Video Exercise for Dr. Churchill

Segment 1 (4-5 mins): What is Alzheimer’s Disease?

Alzheimer disease (AD) is the most common cause of dementia, accounting for an estimated 60–70% of cases worldwide. Around 10% of people aged ≥65 years are thought to have AD; this figure rises to 32% in those aged >85 years, among whom the annual incidence of AD is estimated at 6.48%. Patients with AD present with gradual loss of memory and cognitive functions involving the language, visuospatial and executive domains. The pathological hallmarks of AD in the brain are amyloid-β (Aβ) plaques and abnormal tau tangles. Based on the temporal emergence of amyloid and tau pathologies and evidence that Aβ overproduction leads to AD, the amyloid cascade hypothesis was proposed, which posits that Aβ accumulation is the primary event leading to a cascade of effects that ultimately result in neuronal damage5. However, accumulating evidence suggests that the amyloid cascade alone cannot explain much of the pathogenesis of AD, indicating the involvement of other pathological processes. Following the discovery of elevated levels of inflammatory markers in patients with AD as well as of AD risk genes associated with innate immune functions, inflammation has emerged as a vital player

Aβ accumulation has long been a central and initial event in the pathogenesis of AD. Amyloid precursor protein (APP) is cleaved to generate Aβ peptides, which range from 38 to 43 amino acids. Aβ monomers can bind to one another to form Aβ oligomers, polymers and, eventually, insoluble amyloid plaques. Among these different forms, Aβ oligomers are thought to have the strongest toxicity to neurons. The well-known amyloid cascade hypothesis posits that elevated levels of Aβ lead to subsequent pathological events in AD. However, numerous clinical trials of treatments that aimed to clear various forms of Aβ from the brain in people with AD or mild cognitive impairment (MCI) produced disappointing results: although the patients’ amyloid load was reduced, their cognitive function did not improve.

The other hallmark of AD is neurofibrillary pathology, which includes neuritic plaques, neurofibrillary tangles and neuropile threads, formed by the aggregation of tau protein. Under physiological conditions, modified tau stabilizes microtubules, regulates axonal transport, and maintains DNA structure. The pathological modification of tau can lead to detachment of tau from microtubules, resulting in synaptic loss, neuronal dysfunction, and tau aggregation. Compared with amyloid deposition, tau accumulation in the neocortex is believed to occur later but to correlate more closely with cognitive decline in patients with AD.

Non-scientific Version

In this segment, I want to talk to you about Alzheimer's disease, which is the most common cause of dementia. Dementia is a condition that affects a person's memory and thinking abilities. Alzheimer's accounts for about 60-70% of all dementia cases worldwide.

As people age, the risk of developing Alzheimer's increases. Around 10% of those aged 65 and older are believed to have Alzheimer's. This number goes up to 32% for people over 85 years old. The annual incidence of Alzheimer's in this older age group is estimated to be around 6.48%.

Alzheimer's patients experience a gradual decline in memory and cognitive functions, which include language, spatial awareness, and decision-making abilities.

In the brain, Alzheimer's is associated with the buildup of two key proteins called amyloid-β (Aβ) plaques and abnormal tau tangles. These proteins seem to play a significant role in the disease. Researchers proposed the "amyloid cascade hypothesis," suggesting that the accumulation of Aβ is the main trigger for a chain reaction of events leading to brain damage. However, recent evidence indicates that there are likely other processes involved in the development of Alzheimer's.

Aβ buildup has long been thought to be the starting point of Alzheimer's disease. This protein is produced when a molecule called amyloid precursor protein (APP) is broken down. The resulting Aβ peptides can stick together to form different forms, including Aβ oligomers, polymers, and insoluble amyloid plaques. Among these forms, Aβ oligomers are believed to be the most harmful to brain cells.

While the amyloid cascade hypothesis has been a prominent theory, treatments aimed at reducing Aβ in patients with Alzheimer's have not shown significant improvements in cognitive function, despite lowering amyloid levels in the brain.

Another crucial aspect of Alzheimer's disease is neurofibrillary pathology, involving the tau protein. Under normal conditions, tau helps maintain the structure of brain cells. However, when it becomes modified, tau can detach from brain cell structures and lead to the aggregation of neurofibrillary tangles. These tangles can cause further damage to brain cells, resulting in memory and cognitive problems.

Interestingly, tau accumulation seems to happen later in the progression of Alzheimer's but has a more direct connection to cognitive decline.

In recent years, there has been increasing evidence linking inflammation to Alzheimer's disease. Researchers have discovered elevated levels of inflammatory markers in Alzheimer's patients, and certain genes associated with the immune system have been linked to an increased risk of developing the disease.

In summary, Alzheimer's disease is a complex condition involving the buildup of amyloid-β plaques and abnormal tau tangles in the brain. While these proteins have been central to our understanding of the disease, research suggests that other factors, like inflammation, also play vital roles. Finding effective treatments for Alzheimer's remains a significant challenge, but ongoing research gives hope for better understanding and eventually managing this devastating disease.

Thank you for your attention, and I hope this brief overview has helped shed some light on Alzheimer's disease.

Segment 2 (4-5 mins): What is Precision Medicine?

"Precision Medicine Initiative was established by the National Institute of Health (NIH) in 2015 and numerous other organizations involved in research as a novel method of tackling medicine with a focused and patient-specific approach. These institutes have stated specifically that “developing approaches for treating and preventing disease that take into account individual heterogeneity in the environment, genes, and lifestyle for each person” constitutes PM. This method of practicing medicine has a great deal of potential for addressing the unique characteristics of people with various lifestyle, genetic, and associated comorbidities that could alter their reaction to therapy. Numerous specialties, including cancer and cardiology, have started to devote their efforts toward a more precise means of executing medical procedures since its introduction. Following earlier attempts to classify and combine disease states and treatment possibilities based on the individual diagnosis, PM is now being used in the clinical setting. Examples include using blood type to expedite blood transfusions or choosing appropriate antibiotics based on the drug sensitivity of pathogenic bacteria when diagnosing and treating phenylketonuria in newborns. Some examples include checking for specific gene alterations in the BRCA2 and BRCA1 genes in breast cancer patients or customizing cystic fibrosis treatment to target a specific cause related with the patient’s illness. Numerous high-throughput strategies of characterizing patient biomarkers have been combined with vital advancements in computer-based approaches necessary for assessing the substantial quantity of data created by such techniques to enable the implementation of PM in numerous therapies.

The core component of major government programs to change medical practice is the notion of PM, which explains the widespread impact of increased information on the complex developments connected with a person’s health and for forecasting the effectiveness of therapy. Late onset Alzheimer’s disease (LOAD) is a form of AD that develops after the age of 60. It is the most common form of the disease and accounts for most cases. Risk factors for LOAD include age, genetics, and lifestyle factors such as smoking, high blood pressure, and a lack of physical activity. Numerous studies have examined the part that genetics must play at the start of LOAD; one study estimated that genetics accounted for over 50 percent of the phenotypic variable. The transition from generic risk-lowering strategies to specific interventions focusing on particular risk variables, notably genetics, has not yet been fully accomplished in the field of AD prevention. In this, "risk-lowering” strategies to specific interventions focusing on particular risk variables, notably genetics, has not yet been fully accomplished in the field of AD prevention. In this scenario, the complementary roles of genomic studies, investigation, and analysis of fluid- based biological markers, and multi-modal brain imaging will enable the identification of distinct biological mechanisms and signaling cascades in symptomless individuals at the highest threat for development to clinical benchmarks. Due to the field speculation that initial biomarker-driven personalized therapies may present the best possibility of therapeutic achievement, genomic research has led to the identification of genetic risk factors for Alzheimer’s disease, which can aid in early detection. This paradigm shift is moving away from the traditional “one size fits all” concept in drug research. This will make it possible to recognize and describe disease states at the undetected preclinical phase, where pathophysiology and topographic anomalies occur many years to decades before extreme clinical signs. The transition in brain research and AD toward biomarker-directed, “molecularly” tailor-made treatment for highly effective prevention and treatment options are made possible by the PM strategy."

Non-scientific Version

In this segment, I want to tell you about an exciting initiative called the Precision Medicine Initiative, which was launched in 2015 by the National Institute of Health (NIH) and other research organizations. This approach to medicine focuses on treating each person as an individual, considering their unique genetics, lifestyle, and environment.

The goal of precision medicine is to tailor medical treatments specifically to each person's needs. This is especially important because people can have different responses to therapies based on factors like their genetic makeup, lifestyle choices, and other health conditions they might have.

Doctors and researchers from various fields, including cancer and cardiology, are now working together to implement this more precise way of practicing medicine. Instead of using general treatment plans for everyone, they are customizing treatments based on individual characteristics.

Let me give you a few examples of how precision medicine is being used in practice. Doctors may use a person's blood type to choose the right blood for a transfusion quickly. They can also determine the best antibiotics to treat infections by analyzing the sensitivity of the disease-causing bacteria.

In diseases like breast cancer, doctors can check specific genes, like BRCA1 and BRCA2, to better understand how to treat the cancer. For conditions like cystic fibrosis, treatment can be customized to target the specific cause of the illness in each patient.

To make precision medicine work, researchers are using advanced technologies to analyze lots of data about patients. They are studying biomarkers, which are specific signals in the body that can help identify disease risk or progression. By combining this information with computer-based tools, doctors can provide more personalized and effective treatments.

One area where precision medicine is showing great promise is in the field of Alzheimer's disease, specifically the late-onset Alzheimer's disease (LOAD) that occurs after the age of 60. LOAD is the most common form of Alzheimer's, and its development can be influenced by factors like age, genetics, and lifestyle choices.

Researchers are working hard to understand the genetic factors that contribute to LOAD. They believe that genetics may play a significant role in the disease, accounting for over 50% of the variation seen in different individuals.

By studying the genes associated with Alzheimer's, scientists hope to identify people at high risk for the disease before any noticeable symptoms appear. This way, they can intervene early and provide personalized treatments to prevent or slow down the disease's progression.

The shift towards precision medicine means moving away from the old approach of using the same treatment for everyone. Instead, doctors can now recognize and treat diseases at their earliest stages, long before severe symptoms appear.

This exciting new strategy of precision medicine is bringing us closer to more effective and personalized treatments for a range of medical conditions. It's all about understanding each person's unique characteristics and providing the right treatment at the right time.

As we continue to embrace precision medicine, we can look forward to a future where medical care is more personalized, effective, and focused on individual needs. Thank you for listening, and let's support further research efforts in precision medicine to improve the health and well-being of all people.

Segment 3 (4-5 mins): What ethical concerns should researches considers when applying genetics and precision medicine approaches to Alzheimer’s Disease research?

Most genetic studies have been conducted in populations with European ancestry, thereby limiting direct inferences about risk to other populations. These limitations and the generalizability of our genomic evidence should be considered when discussing the risk associated with genetic variants and polygenic risk scores with patients. Understanding the risk associated with specific loci can facilitate the direct development of risk scores that, in combination with clinical risk factors, can be used to predict the likelihood of developing a given disease like Alzheimer’s. Many studies have highlighted the limitations of applying polygenic risk scores (also known as genome-wide polygenic scores) that have been ascertained from European cohorts to other populations, as these are likely to be biased and reduce predictive accuracy. These biases are thought to relate to several factors, including biases in the allele frequency spectrum of risk variants ascertained in European GWAS, with undiscovered associated variants that are common in non-European populations but rare among Europeans not included in scores; differences in LD structure around the causal variant among populations, leading to error in assignment of appropriate risk scores to the causal allele which may be unknown; and heterogeneity in effect sizes across populations. Given these caveats, understanding, and characterizing genetic risk of disease among diverse populations is essential for the successful application of risk prediction scores as a form of precision medicine among non-European populations. Precision medicine and genetic testing have the potential to advance health care by improving our understanding of diseases, early diagnosis of illness, and tailoring of therapies that could improve health outcomes. However, with this new technology comes the responsibility to carefully consider when and how to use it. Ethically implementing precision medicine requires careful attention. Global differences in the prevalence and distribution of diseases and their risk factors are a complex phenomenon determined by environmental, social, demographic, cultural and genetic factors. Genetic variation at the population level is itself shaped by population history, demography, regional environments, and adaptive evolution. Understanding global genetic diversity and its impact on human health and disease has the potential to provide additional insights into the biological mechanisms underlying disease risk and can help quantify the impact of the interplay between genetic and environmental variation on population-level disease. As such, conducting genomic research in diverse populations across the globe can inform therapeutic development, public health and precision medicine initiatives as well as facilitate global equity in the benefits of genomics.

Non-scientific Version

In this segment, I want to talk to you about genetics and how it relates to precision medicine approaches in the treatment of Alzheimer’s Disease. Most of the genetic studies that have been done focused on people of European ancestry, which means that we have limited information about the risks for other populations. This is important because our genetic makeup can affect our chances of developing certain diseases, like Alzheimer's.

When we talk about genetic risk, it means understanding how certain parts of our DNA, called genetic variants, can influence our likelihood of getting a particular disease. By knowing these risks, doctors can develop risk scores that, when combined with other factors like your medical history, can predict the likelihood of you getting a specific disease.

However, there are some challenges with using these risk scores. The scores that have been developed based on European populations might not work as well for other groups. This is because genetic differences between populations can affect the accuracy of these scores.

One reason for this is that some risk variants might be more common in non-European populations but rare in Europeans. So, these variants might not be included in the risk scores used for Europeans, leading to biased predictions for other groups. Additionally, the genetic patterns around the risk variants can vary among populations, making it harder to assign accurate risk scores.

To make precision medicine work for everyone, we need to understand and study genetic risks in diverse populations. It's crucial for developing accurate risk prediction scores that can be used globally.

Precision medicine and genetic testing have the potential to improve healthcare by helping us understand diseases better, detecting illnesses early, and providing personalized treatments. However, we must use this technology ethically and thoughtfully.

Genetic variation is influenced by many factors, including our history, environment, and cultural background. By studying genetic diversity around the world, we can gain more insights into how genetics affects our health and the impact of the environment on diseases.

Conducting research in diverse populations will not only benefit individual health but also help in developing better treatments and public health initiatives. It's a step towards fairness and equity in the benefits of genetic discoveries for all. Understanding global genetic diversity and its impact on human health and disease has the potential to provide additional insights into the biological mechanisms underlying disease risk and can help quantify the impact of gene-environment variation on population-level disease. As such, conducting genomic research in diverse populations across the globe can inform therapeutic development, public health and precision medicine initiatives as well as facilitate global equity in the benefits of genomics.

In overview, genetics plays a significant role in our health and disease risks. To make precision medicine work for everyone, we need to study and understand genetic diversity across different populations. By doing so, we can improve healthcare, develop better treatments, and ensure that the benefits of genetic research are shared globally.

Thank you for your attention, and let's continue supporting research and initiatives that promote genetic understanding and equity in healthcare.

References

Arafah, A., Khatoon, S., Rasool, I., Khan, A., Rather, M. A., Abujabal, K. A., Faqih, Y. A. H., Rashid, H., Rashid, S. M., Bilal Ahmad, S., Alexiou, A., & Rehman, M. U. (2023). The Future of Precision Medicine in the Cure of Alzheimer's Disease. Biomedicines, 11(2), 335. <https://doi.org/10.3390/biomedicines11020335>

Gurdasani, D., Barroso, I., Zeggini, E., & Sandhu, M. S. (2019). Genomics of disease risk in globally diverse populations. Nature Reviews Genetics, 20(9), 520-535.

Lehmann, L. S., Snyder Sulmasy, L., Burke, W., & ACP Ethics, Professionalism and Human Rights Committee. (2022). Ethical considerations in precision medicine and genetic testing in internal medicine practice: a position paper from the American College of Physicians. Annals of Internal Medicine, 175(9), 1322-1323.

Leng, F., & Edison, P. (2021). Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here?. Nature Reviews Neurology, 17(3), 157-172.